REMARKS

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested. Pursuant to 37 CFR § 1.121, attached as Appendix A is a Version With Markings to Show Changes Made.

The rejection of claims 1-4, 6-9, 19-22, and 24-27 under 35 U.S.C. § 112 (2nd para.) for indefiniteness is respectfully traversed in view of the above amendments.

The rejection of claims 1, 2, 19-22, and 24 under 35 U.S.C. § 102(e) as anticipated by U.S. Patent No. 6,077,680 to Kem et al. ("Kem") is respectfully traversed.

Kem discloses methods and compositions comprising DNA segments and proteins from sea anemone species, particularly toxins, toxin analogs, chemically modified toxin analogs, and genes encoding toxins. In column 3, lines 9-25 of Kem, the use of such toxins to interact with the P region of voltage gated potassium channels which is a short stretch of amino acids between the 5th and 6th transmembrane segments. By contrast, the claimed invention calls for evaluating whether a particular material "binds to the external vestibule portion of the ion channel", where the "external vestibule portion is the portion of the ion channel located between the S5 transmembrane and pore forming region of the ion channel or between the pore forming region and the S6 transmembrane of the ion channel". As shown in Figure 1 and described on page 5, lines 9-17 and page 8, lines 21-24 of the present application, the external vestibule portion and the pore forming region are distinct areas. With regard to Figure 1A, the pore forming region is shown within a box identified as the "P region", while the external vestibule portion is underlined. Figure 1B identifies the external vestibule portion as the amino acids which are shaded. This is entirely consistent with Figure 1A in that the amino acids underlined in the depiction of Kv1.2 are the same as those corresponding to the external vestibule portion in Figure 1B. The outstanding office action indicates that the claims encompass the segment of the ion channel evaluated by Kem, because the claims can be read to define "external vestibule portion" as including the P-region. Claims 1 and 19 have been amended to exclude the P-region from the external vestibule portion. Therefore, applicant respectfully submits that the rejection based on Kem should be withdrawn.

The rejection of claims 1, 2, 19-22, 24, and 25 under 35 U.S.C. § 102(b) as anticipated by Stuhmer et al., "Molecular Basis of Functional Diversity of Voltage-Gated Potassium Channels in Mammalian Brain," EMBO J. 8(11):3235-44 (1989) ("Stuhmer") is respectfully traversed.

Stuhmer describes the cloning and sequencing of cDNAs isolated from a rat cortex cDNA library which encode several potassium channel forming proteins. The outstanding office action cites Stuhmer (page 3242, column 1, last paragraph) as teaching a method of identifying a channel blocker for an ion channel by identifying peptides that bind to the external vestibule portion of the ion channel. However, Stuhmer merely reports that the affinity of an ion channel to a positively charged channel blocker (e.g., the DTX and CTX toxins) may depend on the number and presence of negatively charged amino acids in the extracellular portion of the ion channel. Specific amino acid changes which may affect affinity are identified. Thus, Stuhmer describes surveying the entire extracellular region of the ion channel, including the P-region, for negatively charged amino acids. This study of what changes in the structure of an ion channel will affect affinity of the channel to toxins has nothing to do with the present invention which is directed to a method for identifying, as an ion channel blocker for an ion channel, an antibody, a binding portion of the antibody, a probe, or a ligand that binds to the external vestibule portion of the ion channel and is effective to inhibit ion transport through the ion channel. There is no teaching in Stuhmer that agents which bind to the external vestibule region of an ion channel, in fact, block the channel. Since this reference in no way suggests the claimed invention, the rejection based on it should be withdrawn.

The rejection of claims 1-4, 7-9, 19-22, and 24-27 under 35 U.S.C. § 103 for obviousness over Kem in view of the U.S. Patent No. 5,827,655 to Chandy ("Chandy patent"), Chandy et. al., "A Family of Three Mouse Potassium Channel Genes with Intronless Coding Regions," Science 247:973-75 (1990) ("Chandy article"), Stuhmer, Yatani et. al., "A Monoclonal Antibody to the α Subunit of G_k Blocks Muscarinic Activation of Atrial K^+ Channels," Science 241:828-31 (1988) ("Yatani"), Vassilev et. al., "Identification of an Intracellular Peptide Segment Involved in Sodium Channel Inactivation," Science 241:1658-61 (1988) ("Vassilev"), and Tejedor et. al., "Site of Covalent Attachment of α–Scorpion Toxin Derivatives in Domain I of the Sodium Channel α Subunit," Proc. Nat'l Acad. Sci. USA 85:8742-46 (1988) ("Tejedor") is respectfully traversed in view of the above amendments and the following remarks.

The deficiencies of Kem and Stuhmer are described above.

The Chandy patent relates to the n K^+ channel expression product of the MK3 gene or functionally bioactive equivalent thereof and its uses, particularly in combination with identifying immune response and materials modulating or blocking them. To the extent

that this reference describes identifying materials having a modulating effect on n K^+ channel expression, it involves providing an expression system containing the entire DNA encoding a functional K^+ channel expression product, contacting the expression system or the product of the expression system with one or more materials to determine their modulating effect, and selecting from those materials a candidate capable of modulating n K^+ channel expression (see col. 4, lines 3-14). Thus, the Chandy patent evaluates the effectiveness of an inhibitor against expression of the gene encoding the n K^+ channel expression product. Furthermore there is no indication which portion of expression product is monitored for binding by the inhibitor. By contrast, the present invention only needs to evaluate whether a particular material "binds to the external vestibule portion of the ion channel". No gene expression is called for by the claims, and, contrary to what is stated in the outstanding office action, there is no suggestion that the external vestibule portion is a site that should be monitored for binding of inhibitor candidates. As shown in Figure 1 of Pongs, "Molecular Biology of Voltage-Dependent Potassium Channels," Physiol. Rev. 72(4):S69-S88 (1992) (attached as Exhibit 2 to the September 13, 2001, Amendment), the structure of an ion channel is intricate and has a number of different segments. There is absolutely nothing in the Chandy patent to indicate that binding at the external vestibule portion, as opposed to the S1, S2, S3, S4, S5, or S6 segments, should be monitored for binding activity.

The Chandy article discloses a family of 3 mouse potassium channel genes and their sequences. Nowhere does the Chandy article teach a method of identifying an ion channel blocker for an ion channel by "identifying, as an ion channel blocker for an ion channel, an antibody, binding portion of the antibody, probe, or ligand which antibody, binding portion of the antibody, probe, or ligand binds to the external vestibule portion of the ion channel and is effective to inhibit ion transport through the ion channel" (as set forth in claim 1) or a method of screening a drug for effectiveness as an ion channel blocker for an ion channel, wherein the ion channel has an external vestibule portion by "evaluating the cell to determine if the ion channel blocker candidate binds to the external vestibule portion of the ion channel and inhibits ion transport through the ion channel" (as set forth in claim 19).

Yatani describes a monoclonal antibody that binds to a guanine nucleotide binding protein ("G protein"). However, a G protein is totally unrelated to a voltage-gated potassium channel. This distinction is reflected in Jan et. al., "Annual Review Prize Lecture—Voltage-Gated and Inwardly Rectifying Potassium Channels," J. Physiol. 505.2: 267-82 (1997)("Jan")(attached as Exhibit 3 to the September 13, 2001, Amendment). In

Figure 6 on page 272 of Jan, the structure of a voltage-gated potassium channel is depicted. Meanwhile, in Figure 8B on page 274 of Jan, the distinct structure of the G protein is shown. Moreover, Jan (page 273) teaches that "[i]t appears that the G protein βγ-subunits released by the activated M2 muscarinic acetylcholine receptor (m2 AChR) act directly on the muscarinic potassium channel to cause channel activation". This phenomena and the distinct nature of the voltage-gated potassium channel and the G protein is shown in Figure 8 of Yatani. Thus, Yatani has nothing to do with the present invention's concept of examining the binding of materials to the external vestibule region of an ion channel.

Vassilev relates to the antibodies against a conserved intracellular segment of a sodium channel between transmembrane domains III and IV. This segment is in a completely different location than the outer vestibule portion. In particular, Vassilev's segment SP19 is intracellular (see Figure 1A on page 1658 of Vassilev), while the external vestibule portion, by virtue of its location between the S5 and S6 transmembrane regions has a more external location (see Figure 6 of Jan). Thus, Vassilev has nothing to do with the present invention's concept of examining the binding of materials to the external vestibule region of an ion channel.

Tejedor discloses the covalent attachment of α-scorpion toxin to an extracellular loop between transmembrane helices S5 and S6 of a homologous domain I of the sodium channel α subunit. However, as described *supra* with reference to Figure 1 of the present application, the area between the S5 and S6 segments contain not only the external vestibule region but also the P region. There is no suggestion in Tejedor that the binding of materials to the external vestibule region of an ion channel should be examined. Nowhere does Tejedor teach a method of identifying an ion channel blocker for an ion channel by "identifying, as an ion channel blocker for an ion channel, an antibody, binding portion of the antibody, probe, or ligand which antibody, binding portion of the antibody, probe, or ligand binds to the external vestibule portion of the ion channel and is effective to inhibit ion transport through the ion channel" (as set forth in claim 1) or a method of screening a drug for effectiveness as an ion channel blocker for an ion channel, wherein the ion channel has an external vestibule portion, by "evaluating the cell to determine if the ion channel blocker candidate binds to the external vestibule portion of the ion channel and inhibits ion transport through the ion channel" (as set forth in claim 19). In fact, it was subsequently established that the scorpion toxin of Tejedor binds to the P region -- not the external vestibule portion. See Catterall, et al., "From Ionic Currents to Molecular Mechanisms: The Structure and

Function of Voltage-Gated Sodium Channels," Neuron 26:13-25 (2000) (attached as Exhibit 4 to the September 13, 2001, Amendment), particularly page 14 which refers to various toxins as "pore blockers".

Since neither the Chandy patent, the Chandy article, Yatani, Vassilev, nor Tejedor overcome the above-noted deficiencies of Kem and Stuhmer, this combination of references cannot form a proper basis for rejecting the pending claims.

In view of all the foregoing, it is submitted that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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Michael L. Goldman
Registration No. 30,727

NIXON PEABODY LLP
Clinton Square, P.O. Box 31051
Rochester, New York 14603-1051
Telephone: (585) 263-1304
Facsimile: (585) 263-1600

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APPENDIX A

Version With Markings to Show Changes Made

In reference to the amendments made herein to claims 1, 6, 19, and 20, additions appear as underlined text, while deletions appear as bracketed text, as indicated below:

In the Claims:

Please amend claims 1, 6, 19, and 20 as follows:

1. (Thrice Amended) A method of identifying an ion channel blocker for an ion channel comprising:

providing an external vestibule portion of an ion channel, wherein said external vestibule portion is the portion of the ion channel located between the S5 transmembrane and pore forming region of the ion channel or between the pore forming region and the S6 transmembrane of the ion channel, and

identifying, as an ion channel blocker for an ion channel, an antibody, binding portion of the antibody, probe, or ligand which antibody, binding portion of the antibody, probe, or ligand binds to the external vestibule portion of the ion channel and is effective to inhibit ion transport through the ion channel.

6. (Amended) The method according to claim [5] 3, wherein the ion channel is a Kv ion channel.

19. (Twice Amended) A method of screening a drug for effectiveness as an ion channel blocker for an ion channel, wherein the ion channel has an external vestibule portion, said external vestibule portion being the portion of the ion channel located between the S5 transmembrane and pore forming region of the ion channel or between the pore forming region and the S6 transmembrane of the ion channel, said method comprising:

contacting a cell having an ion channel with a drug which is an ion channel blocker candidate;

evaluating the cell to determine if the ion channel blocker candidate binds to the external vestibule portion of the ion channel and inhibits ion transport through the ion channel; and

identifying a drug which binds to the external vestibule portion of the ion channel and inhibits ion transport through the ion channel as an ion channel blocker.

20. (Amended) The method according to claim 19, wherein the ion channel blocker is an antibody, binding portion of the antibody, probe, or ligand.